UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/978,636	11/25/1997	ELAZAR RABBBANI	ENZ-53(DIV-3	4642

28171 7590 04/04/2007

ENZO BIOCHEM, INC.
527 MADISON AVENUE (9TH FLOOR)
NEW YORK, NY 10022

EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	PAPER NUMBER
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	08/978,636	RABBBANI ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *245-255,258 and 262-269* is/are pending in the application.

4a) Of the above claim(s) *268 and 269* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *245-255,258 and 262-267* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11/25/1997* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/3/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 1/3/2007 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 6/27/2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Applicant has added claims 263-269. Therefore, claims 245-255, 258, and 262-269 are pending in the instant application.

Newly submitted claims 268 and 269 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The invention of claims 245-255, 258, and 262-267 are related to the inventions of claims 268 and 269 as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the

product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the nucleic acid constructs of claims 245-255, 258, and 262-267 can be used as a template for a PCR reaction, which does not involve consideration of the methods of claims 268 and 269.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 268 and 269 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not

commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Applicant's amendments to the claims filed on 1/3/07, with respect to the rejection(s) of claim(s) under 35 U.S.C. 112, 2nd paragraph have been fully considered and are persuasive. Therefore, the rejection has been withdrawn.

Sequence Compliance-Drawings

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because there are sequences in the drawings that do not contain a SEQ ID NO.

A complete response to this office action must correct the defects cited above regarding compliance with the sequence rules and a response to the action on the merits which follows.

The aforementioned instance of failure to comply is not intended as an exhaustive list of all such potential failures to comply in the instant application.

Applicants are encouraged to thoroughly review the application to ensure that the entire application is in full compliance with all sequence rules. This requirement will not be held in abeyance.

Response to Applicants Arguments-- 35 USC § 112

Claims 245-254, 263 and 264 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and is repeated for the same reasons of record as set forth in the actions mailed 5/31/05 and 6/27/06.

Claim 245, and those dependent thereon are drawn to nucleic acid constructs which comprise a nucleic acid sequence that encodes a non-eukaryotic polymerase that further comprises a non-native-intron. Newly added claims 263 and 264 are rejected because they depend from claim 245.

Applicant asserts that adequate support was provided for "non-eukaryotic polymerase" in view of the drawings and points to figures 27-31 and 47. Applicant also points to pages 88 and 89 of the specification. However, upon a review of the specification and drawings, there is inadequate support for the term "non-eukaryotic polymerase". Support in the indicated locations provides only a few examples that are non-eukaryotic, but are not considered to teach the genus of non-eukaryotic. While it is agreed that applicants have provided examples of non-eukaryotic polymerases, such

examples are not considered to support the concept that eukaryotic polymerases were ever intended to bė excluded, or in contrast, that archaeobacteria polymerases were to be included. A few examples of species from very broad genus of non-eukaryotic polymerases are not considered to provide support for the entire genus of non-eukaryotic polymerases, and the rejection is maintained therefore.

Applicant asserts that it is not necessary to provide evidence of intent of exclusion of eukaryotic polymerases. It is applicant's position that by reciting the term "non-eukaryotic polymerase" support needs only to be provided for this term. In response, applicant has not provided support for the term "non-eukaryotic polymerase ", as explained above and contrary to applicant's assertion, it is necessary to provide support for negative limitations that exclude other embodiments. Any negative limitation or exclusionary proviso must have basis in the original disclosure. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. See MPEP 2173.05(i) for further explanation on negative limitations.

Claims 245-255, 258 and 262-267 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention, and is repeated for the same reasons of record as set forth in the actions mailed 5/31/05 and 6/27/06.

Newly added claims 263-267 are rejected for the same reasons.

Applicant asserts that the specification actually does provide guidance as to properties of the intron that would lead to inactivation such as a) having the presence of the intron throw the coding sequence out of frame and/or b) using an intron sequence that has at least one stop codon in frame with the target gene sequence or preferably like the SV40 intron, having a stop codon in all three reading frames. Applicant further asserts that the use of this system would be a general strategy that should work for most proteins regardless of what particular function the protein normally carried out. However, it is important to note that the instant claims are not limited to the embodiments addressed by applicant above. The specification does not provide support for the use of any intron, in any polymerase or any bacteriophage polymerase, or any conditionally toxic gene, in any incompatible cell because the specification provides only minimal prophetic description and no exemplification, of any particular intron, polymerase (including bacteriophage polymerase), or toxic gene, or cells compatible or incompatible for whom known structures exist that could be utilized having the claimed function.

As stated above, the specification provides only minimal prophetic description and no exemplification, of any particular intron, polymerase (including bacteriophage polymerase), or toxic gene, or cells compatible or incompatible for whom known structures exist that could be utilized having the claimed function. The specification

provides for the use of T3, T7 or SP6 polymerases, and also for the use of certain "consensus" splice donor and acceptor sites for inserting introns. Applicants prophetically suggest that intron "insertion at any of these sites in a gene coding region should not affect subsequent removal of the processing element in a compatible cell." (page 84 of the instant specification).

However, there is significant unpredictability in such intron removal, since such a process requires a complex interaction between the nucleic acid construct and the already existent cellular machinery. A review article by Balvay et al. indicates that the splicing machinery is highly dependent upon recognizing and interacting with such secondary structures in making the splice. Balvay et al. indicates that the addition of a secondary structure to an existing mRNA can cause the cell to splice at a point not normally spliced at, while removal of such a structure can cause splicing to be eliminated (for example see pages 165 bridging to 166). Furthermore, Balvay indicates that the exon plays a significant role in splice site recognition by the cellular splicing machinery. Since one of skill would understand that the nucleotides in the exon remain in the mRNA (or ribozyme) after splicing, applicants claimed nucleic acid constructs, *following splicing*, would likely therefore contain elements of these exon recognition sites. Such unpredictability indicates that the genus of nucleic acid constructs comprising any intron in any polymerase (or any bacteriophage polymerase), or any toxic gene, and that are active or inactive depending on whether they are found in cells that are compatible or incompatible is very large. The fact that the specification discloses only prophetic examples and a few species of polymerases and

donor/acceptor splice sites is not considered to constitute a sufficient representative sample of the genus of such constructs.

Although applicant asserts that the examples that Balvay bring up are more in the nature of exceptions to the general rule and that there are normal rules of how and where splicing would occur and are predictable, these are simply assertions that are not supported by the instant specification or the art. The teachings of Balvay et al. support the unpredictability of the splicing mechanism, rather than the presence of "normal rules" that are referred to by applicant. Applicant concludes that Balvay et al. are only saying that sometimes it is not where it would normally be expected to take place. This statement is considered to support the unpredictability of such a mechanism.

Claims 245-255, 258 and 262-267 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention and is repeated for the same reasons of record as set forth in the actions mailed 5/31/05 and 6/27/06.

Newly added claims 263-267 are rejected for the same reasons.

Applicants' specifically claim that the inserted and inactivating intronic sequences will be spliced out, a process the specification indicates will be carried out by the cellular machinery that normally operates to splice introns out of pre-mRNA sequences. Applicants indicate that such splicing restores native activity to previously

inactive proteins. However, the specification as filed does not provide any nucleic acid constructs for which this has actually been shown. Applicant's specification does not provide sufficient guidance or examples that would enable a skilled artisan to make the disclosed nucleic acid constructs containing sequences that are spliced out by cellular machinery. Although the specification prophetically considers and discloses making and using such constructs, such a disclosure would not be considered enabling since introducing intervening sequences into nucleic acids alters their secondary structure, which makes their ability to be cleaved by the splicing machinery unpredictable. The specification has not resolved such issues, since no exemplified constructs that contain intervening sequences and are inactive therefore, and by which later processing inside the cell restores activity. Applicants have simply not shown that such intervening sequences can be spliced out to restore any activity to previously inactive polymerases (or any toxic protein for that matter).

Although applicant asserts that the Balvay et al. reference is not applicable because it merely provides evidence that secondary structures may be involved and describes exceptional situations that may be encountered, Balvay et al. is considered to support the unpredictability of secondary structures of RNA and that such secondary structures have a pronounced effect on RNA splicing. Whether applicant considers the teachings of Balvay et al. to be regarding exceptional circumstances or not, Balvay et al. teach the complexity of secondary structures with regards to splicing and there is nothing in the instant specification or claims that excludes that teachings of Balvay et al. from being applicable.

In particular, it is demonstrated that the complex secondary structures of nucleic acids are responsible for their intron excision activity, and furthermore, that predicting the ability of the cellular splicing machinery to splice out precise intervening sequences from disrupted sequences with variable secondary structures such that native activity is restored is considered unpredictable, because the splicing machinery is sensitive to the presence or absence of such structures.

Applicant relies on Lewin for teachings regarding experiments of splicing out a hybrid intron and teachings that splicing sites are generic, meaning that they do not have specificity for individual RNA precursors and the RNA precursors do not convey specific information (such as secondary structure) that is needed for splicing. The teachings of Lewin et al. do not diminish the unpredictability of the intron splicing mechanism when a non-native intron is inserted into a sequence having secondary structure. Simply because splice sites are generic to different sequences that do not "convey" secondary structure that is needed for splicing does not mean that the mechanism does not encounter problems of unpredictability as taught by Balvay et al.

Furthermore, one or ordinary skill in the art would not be able to recognize which cells are "incompatible" or "compatible", as instantly recited, in view of the teachings of Lewin et al. that are cited by applicant. Specifically, if splicing sites are generic and do not have specificity for individual RNA precursors, as taught by Lewin et al., one would not be able to determine without undue experimentation how such introns would get excised from some cells and not from others, as instantly recited. The instant nucleic

acid construct has to be able to allow excision of the intron in some cells but not in others.

Furthermore, the replacement of even a few nucleotides on an mRNA can abolish all activity of the translated protein. It is maintained that neither the specification nor the prior art arms one of skill with the information necessary to engineer sequences into nucleic acid constructs that will be reliably spliced out to result in a protein with native activity restored.

In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed would therefore require the *de novo* determination of intervening sequences that can be fully spliced out without leaving behind any nucleotides that might interfere with native activity. In the absence of any real guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 263, 266 and 267 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **THIS IS A NEW MATTER REJECTION.**

Claims 263, 266 and 267 were newly added with the claims filed on 1/3/07. Claims 263 and 267 recite, "wherein said incompatible cell is a prokaryotic cell and said compatible cell is a eukaryotic cell" and claim 266 recites "wherein said incompatible cell is a prokaryotic cell". These limitations are considered new matter because the specification does not specifically disclose that the incompatible cells are prokaryotic cells and the compatible cells are eukaryotic cells.

There is no support for these claim limitations in the claimed priority document. Therefore, the effective filing date of claims 263, 266 and 267 is considered, for purposes of prior art, to be 11/25/1997, which is the filing date of the instant application.

A review of the specification does not reveal support for these claim amendments. Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist for each claim limitation added in the amended claims filed on 1/3/07.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is (571) 272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Amy H Bowman
Examiner
Art Unit 1635

JON E. ANGELL, PH.D.
PRIMARY EXAMINER

JON E. ANGELL, PH.D.
PRIMARY EXAMINER

AHB